Journal of the Formosan Medical Association (2016) 115, 163–170

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Lung cancer screening with low-dose computed tomography: Experiences from a tertiary hospital in Taiwan

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Received 4 June 2015; received in revised form 5 November 2015; accepted 10 November 2015

KEYWORDS
low-dose computed tomography;
lung cancer screening

Background/Purpose: Lung cancer screening using low-dose computed tomography (CT) has been reported to reduce lung cancer-specific mortality for smokers at high risk. However, despite different characteristics of lung cancer in Asia, there are few data concerning this specific population for screening. We aim to analyze the performance of lung cancer screening with low-dose CT concurrent with chest radiography in Taiwan, with reference to international experience.
Methods: During the 1-year period from January 2012 to December 2012, we conducted a retrospective, single-center population-based screening program for lung cancer in the setting of annual medical examinations. Participants were asymptomatic adults without prior history of any cancer. Low-dose CT and chest radiography were offered to all individuals. Baseline CT evaluations were defined as positive if any noncalcified nodule $\geq$ 4 mm in diameter, which were then classified as solid, pure ground-glass or partial ground-glass opacity.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.11.007

Results: Of 3339 individuals, we detected 34 cancers, yielding an overall cancer detection rate of 1.02%. There was a particularly high cancer detection rate of 6.2% (8/129) in the high-risk group aged younger than 50 years with a positive family history of all types of cancers in first-degree relatives. Adenocarcinomas accounted for 88% (30/34) of cancers and 99% of them were early-stage (including carcinoma *in situ* and Stage I). The probability of cancers was significant higher in nodules with interval growth (odds ratio 257.89, $p = 0.0002$). There was no significant difference in the probability of cancers between ground glass opacity nodules and solid nodules (odds ratio 1.16, $p = 0.72$). Of all screen-detected cancers, 61.76% (21/34) were chest radiographically occult.

Conclusion: Low-dose CT is effective to detect early lung cancers. Further establishment of selection criteria for lung cancer screening, specifically for Asian individuals, is definitely warranted.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide with > 1.3 million estimated deaths annually.[1] According to the Taiwan National Cancer Registry, lung cancer is the fourth most common form of cancer following breast, colon, and hepatobiliary cancer, and accounts for the 12.09% of total number of newly reported cancers. In Taiwan, lung cancer also ranks the highest in terms of cancer-related mortality and accounts for 19.67% of all cancers in 2012.[2] Despite recent advances in surgical, radiotherapeutic, and chemotherapeutic approaches, the long-term survival of patients with lung cancer remains poor. The 5-year survival rate for lung cancer is only 15.9% in Taiwan, with a median survival of 13.2 months.[3] A key point is that most patients have advanced-stage lung cancer at initial diagnosis, while the opportunity for potentially curative interventions is lost.

In a bid to reduce the mortality of lung cancer, randomized trials have been performed over many years with various methods including the use of chest radiography with or without cytological analysis of sputum specimens. However, the analysis demonstrated that there was no difference in mortality between the screened and the control groups[4–6] and therefore no medical organizations recommend screening with chest radiography. Recently, lung cancer screening using low-dose computed tomography (CT) has been carried out in many countries and reported to be effective in detecting lung cancer at a smaller size and earlier stage. In 2011, the National Lung Screening Trial (NLST), the world's largest randomized CT screening trial, demonstrated a 20% reduction in lung cancer-specific mortality with low-dose CT screening compared to screening by chest radiography in high-risk current and former smokers.[7] Following the publication of the NLST results and subsequent analysis of the NLST cohort, several organizations, including National Comprehensive Cancer Network, American College of Chest Physicians (ACCP), and American Society of Clinical Oncology (ASCO) issued formal guidelines for lung cancer screening respectively with similar recommendations on the primary population for screening.[8,9] Furthermore, other ongoing European randomized lung cancer screening trials will validate the NLST results and also provide information on the optimal length of the screen interval and the mortality benefit compared to control arm in which individuals receive no screening.[10] However, before implementation of low-dose CT for lung cancer screening as a national health policy,[11] there are two major questions that need to be answered directly. First, will other populations at risk of lung cancer rather than tobacco smoking benefit from CT screening? Second, can the NLST results be replicated in the community setting?

We report here the findings of lung cancer screening by a tertiary hospital, including the overall detection rate of lung cancers using low-dose CT screening in a comprehensive self-referral program outside a controlled research setting and to compare differences in the pathologic and imaging findings of detected lung cancers in asymptomatic individuals in Taiwan.

Methods

During the 1-year period from January 1, 2012 to December 31, 2012, we conducted a single-center population-based screening program for lung cancer in the setting of annual medical examinations. The service was provided to inhabitants in Taichung City and employees of the China Medical University Hospital, Taichung, Taiwan on a self-referral basis. Participants were asymptomatic adults aged 18 years or older and had no prior history of any cancer. A history of cigarette smoking was not necessary for entrance into the study. For each individual visiting for annual medical examination, relevant clinical notes, previous operations, family history of all types of cancer in first-degree relatives, and other risk factors for lung cancer including cigarette smoking were documented and a physical examination was performed by a dedicated family physician. All participants were enrolled into the study only after written informed consent.

Screening CT and chest radiography

Low-dose CT and chest radiography were offered to all individuals who joined lung cancer screening. All CT scans were performed on thin-slice (0.625 mm) scanners from different manufacturers (General Electric Medical Systems,

Milwaukee, WI, USA and Toshiba Medical Systems, Tokyo, Japan) with variable numbers of detectors (16—320), from lung apex to base without contrast enhancement. The CT scanners included GE LightSpeed 16 Slice CT scanner, GE BrightSpeed 16 Slice CT scanner, GE LightSpeed VCT 64 slice CT scanner, and Toshiba Aquilion One 320 slice CT scanner. All scans were obtained using a low-dose regimen, with the machine set at 120 kVp, 9 (15 mA/0.6 s) or 21 (35 mA/0.6 s) mAs, 1.5:1 pitch ratio, and 0.6 seconds rotation time. The effective radiation dose ranged from 0.3 mSv to 0.8 mSv. All chest radiographs were acquired using Toshiba KXO-50R Radiographic Systems.

All CT images were interpreted on a dedicated workstation, using a commercially available dedicated software tool (AW 4.6, GE Healthcare) by one of four thoracic radiologists with 2 years, 4 years, 11 years, and 18 years of chest CT imaging experience, respectively. Axial and coronal maximum intensity projection images with slab thicknesses of 5 mm were made on workstation to detect the lung nodules and size measurement step by step. The CT images were interpreted on Totoku grayscale diagnostic monitors (MS33i2, Totoku Electric Co., Tokyo, Japan) with resolutions of 3 megapixels. The images were displayed with the fixed lung window setting (window width, 6000 HU; window level, −600 HU) and mediastinal window (window width, 400 HU; window level, 35 HU).

We evaluated the attenuation (classified into: solid, pure ground-glass, partial ground-glass opacity, or calcified nodules) and size of nodules (according to the longest perpendicular diameter: $<$ 4 mm or $>$ 4 mm). The solid nodules are defined as nodule densities completely equal or higher than pulmonary vessel. Pure ground-glass opacity nodules are the nodules of increased pulmonary attenuation with preservation of the bronchial and pulmonary vascular margins with no completely obscured parenchyma. Partial ground-glass opacity nodules are nodules that have both ground-glass and solid components. Calcified nodules are lung nodules with any patterns of calcifications. Baseline CT evaluations were defined as positive if any non-calcified nodule $\geq$ 4 mm in diameter was identified. Baseline chest radiography evaluations were defined as positive if any visible nodules or other clinical significant abnormalities were identified. Other clinical significant abnormalities include atelectasis, pleural thickening or effusion, hilar or mediastinal lesion, chest wall abnormality, alveolar or interstitial opacities, and fibrosis. All individuals with positive findings detected on baseline CT scans or chest radiographs were automatically referred to appropriate thoracic surgeons or pulmonologists for expert evaluations.

There were weekly multidisciplinary lung cancer meetings where thoracic radiologists, surgeons, and pulmonologists from the China Medical University Hospital jointly reviewed and discussed the management plan of individuals with abnormal CT scans or chest radiographs.

Management recommendations, including follow-up low-dose CT scans, positron emission tomography-CT, immediate transthoracic needle biopsy, video-assisted thoracoscopic surgery, or bronchoscopic biopsy, were made by each attending physicians. The most appropriate approach was selected to suit their practice routine based on a nonscientifically validated, internally developed management algorithm (Figure 1), clinician experience, and decisions of individuals with screening detected nodules. All individuals with screening detected lung cancers were traced and the corresponding low-dose CT scans, chest radiographs, clinical notes, and pathology reports were reviewed.

Results

During the 1-year period from January 1, 2012 to December 31, 2012, 3339 asymptomatic individuals attended our screening program for lung cancer and a total of 3576 low-dose CT scans were performed. There were 1746 men and 1593 women, averaging age 48 years (range, 19—86 years; standard deviation 11.5 years). A total of 22.1% of the patients were aged 30—39 years; 28.7% were aged 40—49 years; 29.3% were aged 50—59 years, and 16.2% were aged 60 years or above. There were 893 former smokers, 845 current smokers, and 1661 never-smokers. There were 129 patients younger than 50 years with a positive family history of cancer who attended for lung cancer screening; they constituted 3.9% of the total attendance (Table 1).

Following the definitions described above, 1279 individuals (38.3%) had positive baseline CT findings. During the study period, 237 individuals underwent follow-up low-dose CT scans, which were performed 3 months or 6 months after the initial examinations. As a result of abnormal findings described at the baseline and follow-up low-dose CT scans, 41 individuals underwent immediate or delayed diagnostic evaluation with surgical removal of the nodule, which was followed by curative pulmonary resection if the presence of malignancy was documented at frozen resection. Figure 2 indicates the follow-up and outcomes of individuals examined.

Of 3339 individuals undergoing low-dose CT for lung cancer screening during the study, we detected 34 cancers, which gave an overall cancer detection rate of 1.02% (Table 2). The age range of the patients detected with cancers was 26—72 years with a median of 47 years. Of the 34 screening-detected cancers, 11 (32%) cancers were found in never-smokers, seven (20%) cancers were found among former smokers, and 16 (47%) cancers were found in current smokers. Our cancer detection rate was 1.35% (10 of 739) in the age-group 30—39 years, 0.94% (9 of 958) in the age-group 40—49 years, and 0.92% (14 of 1518) in the age-group 50 years or above. In our study, there was a particularly high cancer detection rate of 6.2% (8 of 129) in the high-risk group aged younger than 50 years with a positive family history of first-degree relatives having cancers.

Of the 34 screening-detected cancers on CT scans, cancers presented as pure ground-glass opacity nodules in 22 patients, partial ground-glass opacity nodules in two patients, and solid nodules in 10 patients. In order to reduce bias, the difference in the probability of cancers between ground-glass opacity and solid nodules, was calculated only on the basis of individuals who had received regular follow-up or management included (Figure 2). The probability of cancers was higher in ground-glass opacity nodules (24 of 119, 20.17%) than in solid nodules (10 of 56,

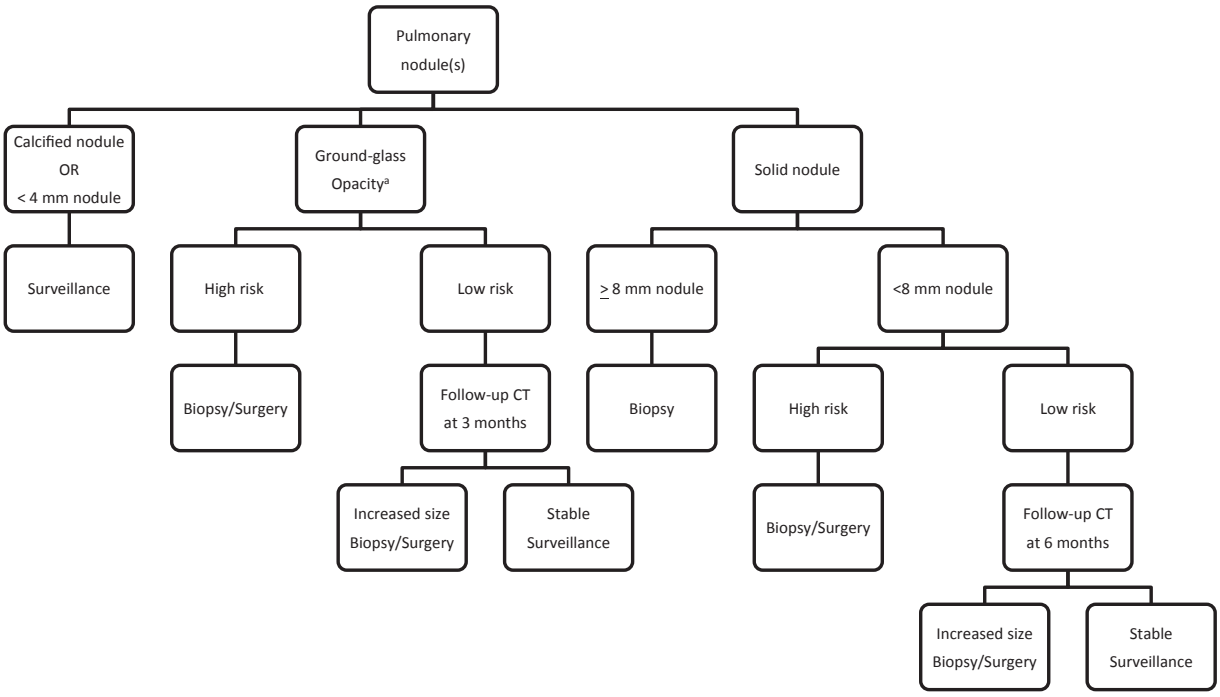

Figure 1 Management algorithm for pulmonary nodules detected by low-dose computed tomography (CT) scans. Recommendation is based on the attenuation and size of nodules. Risk stratification is determined by age, cigarette history, and family history of cancers. The high risk group includes any of the following criteria: beyond age 50 years, history of cigarette smoking, or presence of family history of cancer. The low risk group is defined as none of above. [a]Nodules with ground-glass opacity include nodules with pure and partial ground-glass opacity.

Table 1 Characteristics of the study population.

Factor	Description	*n*	(%)
Sex	Male	1746	(52.3)
	Female	1593	(47.7)
Age group (y)	19—29	124	(3.7)
	30—39	739	(22.1)
	40—49	958	(28.7)
	50—59	978	(29.3)
	60—69	414	(12.4)
	70—79	115	(3.4)
	80—89	11	(0.3)
Cigarette history	Never-smoker	1601	(47.9)
	Former smoker	893	(26.7)
	Current smoker	845	(25.3)
Family history of cancers	Present	129	(3.9)
	Absent	3210	(96.1)

17.86%) but this was not statistically significant (odds ratio 1.16, $p = 0.72$).

All the cancers were detected from the prevalent (1st) round of screening, while the majority of them (27 of 34, 79.41%) were diagnosed after follow-up low-dose CT scans. Of these, the probability of cancers was significantly higher in nodules with interval growth (13 of 13, 100%) than in nodules without interval change (14 of 152, 9.21%; odds ratio 257.89, $p < 0.001$). So far, we have not encountered any cases of interval cancers (i.e., lung cancers that presented and were diagnosed during the follow-up period and not detected by our screening program) during the study period.

Pathology reports of these 34 screening-detected cancer patients were available for review. Of the 34 patients with cancers, 30 (88%) had adenocarcinomas, three (8%) had invasive thymoma, and one (3%) had a germinoma. Of the 30 patients with adenocarcinoma, adenocarcinoma *in situ* was seen in 12 (40%), Stage IA (14 T1a and 2 T1b) in 16 (53.3%) patients, Stage IB in one (3.3%) patient, and Stage IIIA in one (3.3%) patient. All of them underwent potentially curable pulmonary resection via video-assisted thoracoscopy and four patients received adjuvant chemotherapy. During the study period, there have been no major complications documented following an invasive procedure for a positive CT finding thus far.

Abnormal findings including visible nodules and other clinical significant abnormalities were detected by chest radiographs in 477 (14.03%) of these asymptomatic individuals. Of 477 individuals with abnormal findings detected by chest radiographs, 21 (4.4%) had visible nodules and 456 (95.6%) had other clinical significant abnormalities. Thirteen of 477 individuals with abnormal findings detected by chest radiographs had cancers, which gave a cancer detection rate of 2.73%. However, 21 of 2862 individuals with normal chest radiographs had cancers and thus 61.76% (21 of 34) of all screening-detected cancers were chest radiographically occult. Table 3 indicates the screening performance during the study period.

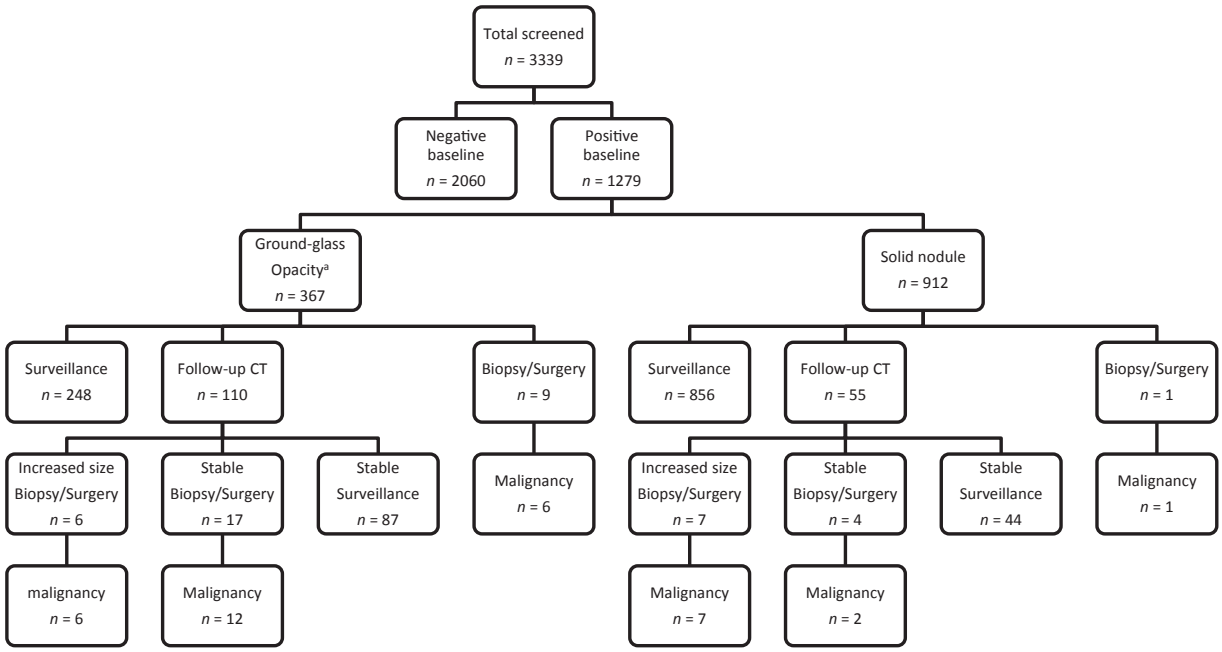

Figure 2 Follow-up and outcome of baseline low-dose computed tomography (CT) scans. [a]Nodules with ground-glass opacity include nodules with pure and partial ground-glass opacity.

Discussion

Recently, the analysis from NLST reported favorable efficiency and cost-effectiveness results for lung cancer screening with low-dose CT.[12] Meanwhile, more and more evidence from other ongoing high-quality randomized controlled trials[13,14] will demonstrate the benefits of low-dose CT, based on reports of significant reductions in mortality to validate the NLST results. However, most of these studies were conducted for individuals with a history of cigarette smoking in North America and Europe.[15,16] Furthermore, the epidemiological, demographic, clinical, and histological features of lung cancer, and the cost associated with lung cancer screening and health care setting in these countries are considered to be different from Taiwan.[17,18] These considerations prompted us to evaluate the performance of lung cancer screening with low-dose CT in the setting of annual medical examinations in Taiwan.

In our study, the overall cancer detection rate by low-dose CT (1.02%) was lower than previously reported (3.3%) in the Early Lung Cancer Action Project study.[19] We offer two possible explanations. First, all the participants in our study attended for screening on a voluntary, self-referral basis. The recruitment criteria did not have any restriction on the population potentially at high risk of lung cancer because of age and a history of cigarette smoking. As a result, 1601 (47.95%) never-smokers and 1699 (49.98%) individuals aged younger than 50 years of our study population would be considered as low-risk group and routine lung cancer screening would not be recommended according to the National Comprehensive Cancer Network guidelines. Consistent with this explanation, the overall cancer detection rate was also lower (0.36—1.1%) in the Japanese[20] and Korean studies.[21] Second, in the setting with only passive follow-up, there was a large recognition gap between individuals' preference, compliance, and management recommendations. Therefore, the cancer detection rate might be underestimated to an unknown degree since not all individuals with positive CT findings and concomitant high-risk features, including nodules with ground-glass opacity and interval growth, would receive diagnostic evaluation eventually.

Our first important finding is that the cancer detection rate in the group aged younger than 50 years with family history of all types of cancers in first-degree relatives, regardless of smoking status, was particularly high (6.2%). In Asia, patients with lung cancer tended to have a younger age of onset and about 30% of them were never-smokers.[22] In the meanwhile, besides tobacco smoking,[23] it has also been described that family history of cancers was associated with risk of lung cancer and risk appeared to be greater in those with relatives with early age at diagnosis or multiple affected family members.[24] Despite the controversial relationship between ethnicity, young age, family history, and never-smokers, other different environmental exposure and genetic susceptibility might play important roles in the connection of these four conditions and the development of lung cancer.[25] The intention of our study is to highlight that a different selection criteria for lung cancer screening in Asian has the potential to be a worthwhile health care strategy.

The second important finding is that concomitant features of CT scan, including nodules with and interval growth, indicated a significant positive association with lung cancer. The odds ratio for nodules interval growth related to lung cancer was 257.89. Previous studies had similar results, strengthening the conclusion that visual characteristics and descriptors were helpful in management of nodules detected on CT scans under the current

Table 2 Characteristics of detected lung cancers by low-dose CT screening.[a]

No.	Sex	Age (y)	Types of attenuation	Histology	TNM	Stage	Treatment
1	Female	50	12 mm GGO, RUL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
2	Male	37	6.5 mm GGO, RUL	Adenocarcinoma *in situ*	TisN0M0	0	Lobectomy
3	Female	37	10 mm GGO, LUL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
4	Male	50	8.5 mm GGO, LUL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
5	Female	44	9 mm GGO, LUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
6	Female	46	17 mm solid, RML	Adenocarcinoma	T1aN0M0	IA	Lobectomy
7	Female	54	7 mm GGO, RUL	Adenocarcinoma	T1aN0M0	IA	Wedge resection
8	Male	35	7.5 mm GGO, RLL	Adenocarcinoma	T1aN0M0	IA	Wedge resection
9	Female	47	10 mm GGO, LUL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
10	Male	64	19 mm GGO, RLL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
11	Female	48	7.5 mm GGO, LLL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
12	Female	51	6.5 mm GGO, RML	Adenocarcinoma	T1aN0M0	IA	Wedge resection
13	Male	52	18 mm solid, RML	Adenocarcinoma	T1bN0M0	IA	Lobectomy
14	Female	50	8.2 mm GGO, LLL	Adenocarcinoma	T4N0M0	IIIA	Lobectomy
15	Male	72	10 mm solid, LLL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
16	Female	34	8 mm GGO, LLL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
17	Female	35	8 mm GGO, RUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
18	Male	60	8 mm GGO, RUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
19	Female	56	23 mm solid, LLL	Adenocarcinoma	T1bN0M0	IA	Lobectomy
20	Female	65	12 mm solid, LLL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
21	Male	33	7 mm GGO, LLL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
22	Female	42	7.5 mm GGO, RLL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
23	Male	39	7 mm GGO, LUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
24	Male	72	9 mm GGO, LUL	Adenocarcinoma	T1aN0M0	IA	Wedge resection
25	Female	47	10 mm GGO, LUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
26	Female	43	7 mm GGO, LUL	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
27	Female	62	7 mm GGO, RLL	Adenocarcinoma	T2aN0M0	IB	Lobectomy
28	Female	44	18 mm solid, RLL	Adenocarcinoma	T1aN0M0	IA	Lobectomy
29	Female	37	9 mm GGO, RML	Adenocarcinoma *in situ*	TisN0M0	0	Wedge resection
30	Male	61	9 mm GGO, LLL	Adenocarcinoma	T1aN0M0	IA	Wedge resection

GGO = ground-glass opacity; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; Tis = carcinoma *in situ*.

[a] Of the 30 patients with screening-detected lung cancers, 14 underwent thoracoscopic lobectomy and 16 underwent thoracoscopic wedge resection. All of them underwent hilar and mediastinal lymph nodes dissection at the same time with pulmonary resection. Nodules with ground-glass opacity include nodules with pure and partial ground-glass opacity.

Table 3 Performance characteristics of screening methods.

	True positive	False negative	False positive	True negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Low-dose computed tomography	34	0	1245	2060	100	62.3	2.7	100
Chest radiography	13	21	464	2841	38.2	85.9	2.7	99.3

practice.[26,27] Further technologies used to aid decision making, including quantitative and multimodality approach, will become widespread in the near future.

Regarding the management algorithm of our study, 80.49% (34 of 41) of individuals who received diagnostic evaluation, were diagnosed as cancer eventually. As in most previous studies,[28] adenocarcinomas were oversampled with approximately two- to three-fold, accounting for 88% (30 of 34) of cancers in our study population. Among those with adenocarcinoma, adenocarcinoma *in situ* was seen in 12 (40%), Stage IA (14 T1a and 2 T1b) in 16 (53.3%) patients, and Stage IB in 1 (3.3%) patients. Compared with previous Western and Japanese studies,[29] the percentage of early-stage lung (96.6%, including carcinoma *in situ* and Stage I) was higher and almost all adenocarcinomas in our study were potentially curable after pulmonary resection. Despite particularly early diagnosis of lung cancer, our management algorithm still provided a high enough positive predictive value for any positive finding that led to diagnostic evaluation.[30]

Although annual screening with chest radiograph did not reduce lung cancer mortality by the Prostate, Lung,

Colorectal, and Ovarian cancer screening trial,[31] with respect to the existing results of the NLST, there are still many debates over implementation of low-dose CT for lung cancer screening as a national health policy. The potential shortcomings include false-positive results, financial costs, radiation exposure, and unnecessary numerous diagnostic workups and complications from the procedures.[32] By contrast, chest radiograph could be another *screening tool of choice* for early detection of lung cancer without the additional shortcomings of low-dose CT. Furthermore, a recent population-based cohort study demonstrated an 18% reduction of lung cancer mortality with chest radiograph screening.[33] However, our study showed that 61.76% of all screen-detected cancers were chest radiographically occult, suggesting that chest radiograph alone may not be sufficient to exclude malignancy. Its exact application remains to be determined in the future.

Notwithstanding the comparative results, there were several limitations associated our screening program. First, self-referral setting with self-paid medical expenses of low-dose CT invariably attracted individuals with more health consciousness, suggesting selection bias in our study. Second, not all individuals with positive baseline CT findings received regular follow-up and management as recommendation. They had free choices to seek second opinions or diagnostic evaluations in other hospitals, partly because of convenience in accessing medical care in Taiwan. Therefore, there might be some patients having lung cancers that were detected by our baseline CT scans but not included in the present study. The third limitation was that our study period was short (18 months at most) compared with NLST and other ongoing European randomized lung cancer screening trials (3 years at least), and, thus, the overall cancer detection must be underestimated. It seemed difficult to correct the *true* cancer detection rate on the current retrospective basis and the subsequent influence on the importance of family history of cancer and interval growth was unpredictable.

We defined family history of cancer as the presence of first-degree relatives with all types of cancer in our study. However, several potential limitations about family history of cancer in our study should be also considered. First, family history of cancer was assessed using self-administered questionnaires but not the cancer registry database. The accuracy of self-reported data may not always be satisfactory. Second, detailed information on age at diagnosis and cell type of cancer was not collected completely. In our study, we can only highlight the high detection rate in young and middle-aged individuals with a family history of cancer. Further investigation on the association of lung cancer risk with family history of different types of cancer is definitely warranted to improve clinical practice.

In conclusion, our study qualified the efficiency of low-dose CT to detect early lung cancers. Moreover, the result demonstrated that a particularly high detection rate in young and middle-aged individuals with a family history of cancers. Therefore, further establishment of selection criteria specifically for Asian individuals and lung cancer screening protocols with systems integration by government are definitely warranted to improve cost-effectiveness and outcomes for lung cancer patients.

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